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**Embolic strokes of undetermined source:
Prevalence and patient features in the ESUS Global Registry**

Kanjana S. Perera, M.B., B.S.
Department of Medicine (Neurology)
McMaster University
Hamilton Health Sciences
Hamilton, Ontario, Canada

Thomas Vanassche, M.D.
Department of Cardiovascular Sciences
University of Leuven
Leuven, Belgium

Jackie Bosch, Ph.D.
Population Health Research Institute McMaster University
Hamilton Health Sciences
Hamilton, Ontario, Canada

Mohana Giruparajah, B.Sc
Population Health Research Institute McMaster University
Hamilton Health Sciences
Hamilton, Ontario, Canada

Balakumar Swaminathan, M.Sc
Population Health Research Institute McMaster University
Hamilton Health Sciences
Hamilton, Ontario, Canada

Katie R. Mattina, B.Sc
Population Health Research Institute McMaster University
Hamilton Health Sciences
Hamilton, Ontario, Canada

Scott D. Berkowitz, M.D.
Bayer Healthcare Pharmaceuticals
Whippany, New Jersey, USA

Antonio Arauz, M.D.
Instituto Nacional de Neurología y Neurocirugía
Mexico D.F., Mexico

Martin J. O'Donnell, M.B.B.S.
University of Galway
Galway, Ireland

Sebastian F. Ameriso, M.D.
Institute for Neurological Research
Fundacion para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI)
Buenos Aires, Argentina

Graeme J. Hankey, M.D.
School of Medicine and Pharmacology

University of Western Australia
Sir Charles Gairdner Hospital
Perth, Australia

Byung-Woo Yoon, M.D.
Department of Neurology
Seoul National University Hospital
Seoul, Korea

Philippa Lavalley, M.D.
Department of Neurology
Bichat Hospital
Paris, France

Luis Cunha, M.D.
Centro Hospitalar e Universitário de Coimbra
Coimbra, Portugal

Nikolay Shamalov, M.D.
Pirogov Russian National Research Medical University
Moscow, Russia

Raf Brouns, M.D.
Universitair Ziekenhuis Brussel
Brussels, Belgium

Rubens J. Gagliardi, M.D.
Irmandade da Santa Casa de Misericórdia de São Paulo
Sao Paulo, Brazil

Scott E. Kasner, M.D.
Department of Neurology
Hospital of the University of Pennsylvania
Philadelphia, United States

Alessio Pieroni, M.D.
Department of Neurology and Psychiatry
“Sapienza” University of Rome
Rome, Italy

Philipp Vermehren, M.D.
Department of Neurology
University Hospital Heidelberg
Heidelberg, Germany

Kazuo Kitagawa, M.D.
Department of Neurology
Tokyo Women’s Medical University
Tokyo, Japan

Yongjun Wang, M.D.
Department of Neurology
Beijing Tiantan Hospital
Capital Medical University
Beijing, China

Keith Muir, M.D.
Institute of Neuroscience and Physiology
University of Glasgow
Queen Elizabeth Hospital
Glasgow, United Kingdom

Jonathan Coutinho, M.D.
Academic Medical Center
Amsterdam, Netherlands

Ildiko Vastagh, M.D.
Department of Neurology
Semmelweis University
Budapest, Hungary

Stuart J. Connolly, M.D.
Department of Medicine (Cardiology)
Population Health Research Institute
McMaster University
Hamilton Health Sciences
Hamilton, Ontario, Canada

Robert G. Hart, M.D.
Department of Medicine (Neurology)
Population Health Research Institute
McMaster University
Hamilton Health Sciences
Hamilton, Ontario, Canada

On behalf of the ESUS Global Registry Investigators
(see Appendix 1 for full listing of investigators)

Address correspondence to:
Robert G. Hart, M.D.
Population Health Research Institute
DBCVSRI C4-105
237 Barton Street East
Hamilton, Ontario L8L 2X2 Canada
Email: robert.hart@phri.ca
Telephone: 905-521-2100 ext 41152
Fax: 905-577-1427

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Abstract

Background:

Recent evidence supports that most non-lacunar cryptogenic strokes are embolic. Accordingly these strokes have been designated as embolic strokes of undetermined source (ESUS).

Aims:

We undertook an international survey to characterize the frequency and clinical features of ESUS patients across global regions.

Methods:

Consecutive patients hospitalized for ischemic stroke were retrospectively surveyed from 19 stroke research centers in 19 different countries to collect patients meeting criteria for ESUS.

Results:

Of 2144 patients with recent ischemic stroke, 351 (16%, 95% CI 15% to 18%) met ESUS criteria, similar across global regions (range 16% to 21%), and an additional 308 (14%) patients had incomplete evaluation required for ESUS diagnosis. The mean age of ESUS patients (62 years; SD=15) was significantly lower than the 1793 non-ESUS ischemic stroke patients (68 years, $p \leq 0.001$). Excluding patients with atrial fibrillation ($n = 590$, mean age = 75 years), the mean age of the remaining 1203 non-ESUS ischemic stroke patients was 64 years ($p=0.02$ vs. ESUS patients). Among ESUS patients, hypertension, diabetes, and prior stroke were present in 64%, 25% and 17%, respectively. Median NIHSS score was 4 (interquartile range 2-8). At discharge, 90% of ESUS patients received antiplatelet therapy and 7% received anticoagulation.

Conclusions:

This cross-sectional global sample of patients with recent ischemic stroke shows that one-sixth met criteria for ESUS, with additional ESUS patients likely among those with incomplete diagnostic investigation. ESUS patients were relatively young with mild strokes. Antiplatelet therapy was the standard antithrombotic therapy for secondary stroke prevention in all global regions.

Introduction:

Cryptogenic strokes are strokes of otherwise undetermined cause and comprise about 25% all ischemic strokes.(1,2) There is evidence that most non-lacunar cryptogenic strokes are embolic based on an “open artery” supplying the area of brain infarction.(3) It has long been recognized that identification of the source of the embolus is often not possible, even at autopsy.(4,5) Advances in diagnostic techniques have identified a substantial number of potential sources of embolism in patients with non-lacunar cryptogenic stroke.(1) Multiple potential embolic sources (e.g. a patent foramen ovale, left atrial stasis, aortic arch atherosclerosis) are often present in an individual patient, and identifying the culprit lesion cannot be done with certainty. This uncertainty has forestalled the development of randomized trials, and there has been little progress in secondary prevention of cryptogenic stroke in recent decades.

Embolic strokes of undetermined source (ESUS) have in common thromboembolic mechanisms that may be more responsive to anticoagulants than antiplatelet therapy for secondary stroke prevention.(1) This is the basis for two large international randomized trials now ongoing that are comparing new selective oral anticoagulants with aspirin.(6,7)

Relatively little is known about the frequency or clinical features of ESUS patients.(8) We undertook a global survey to determine the fraction of patients with acute ischemic stroke who meet criteria for ESUS and to characterize features of ESUS patients in different countries and across global regions.

Methods:

Consecutive patients with recent ischemic stroke were sought at 20 stroke research centers in 20 different countries, targeting review of 100 patients with acute ischemic stroke at each site or until 25 patients meeting ESUS criteria were identified.

Investigators were selected based on participation on the Cryptogenic Stroke / ESUS International Working Group (1) and on regional distribution in countries involved in the NAVIGATE ESUS international randomized trial.(6) Sites were instructed to retrospectively identify consecutive inpatients evaluated for recent stroke in 2013- 2014

either from hospital discharge diagnosis codes or from databases associated with acute stroke units. Criteria for ESUS were those previously published.(Table 1)(1) A 9-page case report form was completed for each ESUS patient by a physician provided with specific instructions and definitions. The study was compliant with local institutional research board regulations; informed consent was not required at any site for this anonymized data collection based on medical record review.

Data were analyzed according to five global regions: Europe, North America, Latin America, East Asia, and Pacific. Data from one site (Budapest, Hungary) were not included in the analyses because cardiac rhythm monitoring required for diagnosis of ESUS was not routinely carried-out (i.e. no patients met criteria for ESUS). Minor-risk cardioembolic sources were those previously described.(1)

Case report forms were entered into a central database via on-line data entry or via an automated fax-based data entry system. Missing data were queried, and final data were exported to STATA 13.0 for statistical analysis. Descriptive analyses regarding the frequency of key features were done using T-test and Chi-square; and limited multivariate models were done to identify independent associations.

Results:

Frequency of ESUS by country and global region

Of 2144 patients with recent ischemic stroke collected from 19 stroke research centers in 19 countries, 351 (16%, 95%CI 15% to 18%) met ESUS criteria, ranging widely from 1% in Amsterdam to 36% in Paris.(Table 2) Of note, echocardiography (required for diagnosis) was not routinely carried-out in ischemic stroke patients in Amsterdam (done in 26% of ischemic stroke patients): excluding this site, the frequency of ESUS was 17%. Excluding 308 (14%) patients with incomplete evaluation required for ESUS diagnosis,(Figure) the frequency of ESUS was 19%.

Among patients meeting criteria for ESUS, 40% underwent only 24-hour Holter monitoring, 33% had only >24 hours of inpatient cardiac telemetry, 19% had both 24-

hour Holter monitoring and inpatient cardiac telemetry, and 8% had either >24 hours of Holter monitoring or non-telemetry extended (>24 hours) of cardiac rhythm monitoring.

Comparison of the frequency of ESUS according to global region was limited by small numbers of strokes and centers, but it was relatively uniform: 16% in all regions except East Asia (21%).(Table 3)

Reasons that ischemic stroke patients did not meet ESUS criteria

The most frequent reason that patients with ischemic stroke did not meet criteria for ESUS was identification of atrial fibrillation (n=590, 28% of all ischemic strokes). Additional reasons were visualized lacunar (small subcortical) infarcts (n=339, 16%), ipsilateral cervical carotid stenosis $\geq 50\%$ (n=293, 14%), and absence of required visualization of index stroke on neuroimaging (n=115, 5%).(Figure) In the remaining patients (n=308, 14%), insufficient evaluation was completed to assess the criteria required for ESUS diagnosis. For those with insufficient diagnostic testing to meet ESUS criteria, the mean age was 66 years, and 30-day mortality was 7%.

Age and sex distribution of ESUS patients

The mean ages of ESUS patients varied across sites: Beijing had the youngest mean age (48 years) and Brussels the oldest (74 years). Overall, the age of the 351 ESUS patients averaged 62 years (SD=15), but the mean age was younger (56 years) at the three East Asian sites vs. others (65 years)($p=0.002$). (Table 4). The mean age of the ESUS patients was significantly lower than in the 1793 non-ESUS ischemic stroke patients (mean age 68 years, $p \leq 0.001$). When patients with atrial fibrillation were excluded (n=590, mean age = 75 years), the mean age of the remaining 1204 non-ESUS ischemic stroke patients without atrial fibrillation was 64 years ($p=0.02$ vs. ESUS patients). Overall, 57% of ESUS patients were men, with sex distribution similar across global regions with the exception of 78% men at the three East Asian sites.(Table 4)

Other clinical features of ESUS patients

Among the 351 ESUS patients, hypertension, diabetes, and coronary artery disease were present in 64%, 25%, and 10% respectively; 31% were taking antiplatelet therapy at stroke onset.(Table 4) Seventeen percent of the ESUS patients had a history of stroke or TIA prior to the index stroke. Median (IQR) NIHSS score near hospital admission was 4 (interquartile range 2-8); 16% received intravenous tPA at the time of the index stroke. MRIs were done in 77%, with an old ischemic stroke (i.e. prior to index stroke) present on MRI in 40%. Transesophageal echocardiography (TEE) was undertaken in 35% of ESUS patients, with complex aortic arch plaque reported in 6% of those undergoing TEE.(Table 4) The 30-day mortality rate was 2% in ESUS patients compared with 10% in stroke patients with identified atrial fibrillation, and 5% in non-ESUS, non-atrial fibrillation patients. Contraindications to anticoagulant therapy were identified in 9%. At hospital discharge, 90% of ESUS patients received antiplatelet therapy, 7% anticoagulant therapy and 3% no antithrombotic therapy.(Table 4)

Frequency of minor-risk potential embolic sources in ESUS patients

Of ESUS patients with anterior circulation stroke, 79% had non-stenotic cervical carotid artery plaques with a mean diameter stenosis of 17%. Among those who underwent transthoracic (precordial) echocardiography, mitral annular calcification or myxomatous changes, aortic valve stenosis or calcification, and hypokinetic/ akinetic left ventricle were detected in 5%, 7%, and 4%, respectively. Of the ESUS patients who underwent transesophageal echocardiography, aortic arch atherosclerotic plaques were present in 29% and patent foremen ovale in 25%. Seventy-four per cent of ESUS patients had at least one minor-risk potential embolic source identified, and 24% had two or more.(Table 5)

Discussion:

This global survey found that ESUS patients comprise about one in six ischemic strokes at large international stroke centers (and likely higher at centers that routinely undertake the complete evaluation required to meet ESUS criteria). ESUS patients on average had relatively minor strokes with a low 30-day mortality rate (3%), and their mean age (62 years) was similar to, but significantly lower than, that of non-ESUS stroke patients

without atrial fibrillation (64 years). The frequency and clinical features of ESUS patients were generally similar across global regions. Most (74%) ESUS patients had at least one minor-risk embolic source identified that could have been the cause of stroke, and nearly a quarter (24%) had two or more potential embolic sources identified. Interestingly, the prevalence of patent foramen ovale among ESUS patients undergoing transesophageal echocardiography (25%) was not increased over that expected in the general population.

Excluding patients who did not undergo the complete diagnostic investigation required for ESUS diagnosis (n=308, most often lack of intracranial arterial imaging), the frequency of ESUS was 19%. Considering an estimated 25% frequency of cryptogenic ischemic strokes based on the recent literature,⁽¹⁾ this frequency of ESUS supports the notion that most (but not all) non-lacunar cryptogenic ischemic strokes are likely due to embolism.

The mild severity of stroke in ESUS patients is consistent with smaller emboli originating from cardiac valves and arterial sources, in contrast to larger emboli that typically originate in the cardiac chambers (e.g. left atrial thrombi in patients with atrial fibrillation.⁽⁹⁾ Our observations regarding stroke severity are consistent with those regarding ESUS patients from the Athens Stroke Registry.⁽⁸⁾ The substantially younger age and milder strokes of ESUS patients compared with patients with atrial fibrillation-associated stroke support different embolic origins (i.e. that undiagnosed paroxysmal atrial fibrillation is unlikely to underlie most ESUS). Alternatively, younger stroke patients may more often undergo the complete diagnostic evaluation required to meet ESUS criteria. Similarly, ischemic stroke patients with more severe strokes and/or early in-hospital mortality may not have undergone all of the required diagnostic testing.

Of interest, atrial fibrillation was identified in 28% of consecutive ischemic stroke patients, a higher fraction compared with hospitalized stroke patients in past decades (typically between 15-20%) probably due to both increasing vigilance and prevalence. Recent studies suggest that prolonged (>1 month) cardiac rhythm monitoring identifies additional patients with cryptogenic stroke who have episodes of paroxysmal atrial

fibrillation,(10,11) often very brief and of uncertain etiologic relevance.(12) Small subcortical “lacunar” infarcts were visualized in 16% of ischemic stroke patients and excluded the diagnosis of ESUS; unidentified lacunar infarcts were likely over-represented among the additional 5% of patients with non-visualization of strokes on neuroimaging.(Figure)

Limitations of this study include participation by a limited number of selected, high-volume stroke centers. A single site in each country may not accurately reflect the spectrum of stroke. However the study sites represented many global regions allowing characterization of ESUS patients around the world. To ensure data quality in this retrospective study, standardized data collection forms were used along with specific definitions.

Antiplatelet therapy was used for secondary stroke prevention in 90% of ESUS patients, in-line with recent guideline recommendations.(13-15) Although emboli vary in composition, almost all include, in whole or in part, thrombus, and it has been proposed that anticoagulants could offer more protection against recurrent stroke for ESUS patients than antiplatelet agents.(1) Contraindications to anticoagulation were identified in relatively few (about 10%) ESUS patients. Currently, two large international randomized trials are underway comparing an oral factor Xa inhibitor and direct thrombin inhibitor, respectively, with aspirin for secondary prevention of stroke in ESUS patients, (6,7) as well as another phase II randomized trial.(16)

In summary, this study provides a benchmark for the global frequency and clinical features of patients with ESUS. This contemporary cross-sectional sample shows generally consistent clinical features of the ESUS patients across global regions. ESUS patients comprise an important subset of ischemic stroke patients around the world: 16% fulfilled all diagnostic criteria for ESUS with additional ESUS patients likely among the 14% with incomplete diagnostic investigation. The unresolved issue of anticoagulant vs. antiplatelet prophylaxis for optimal secondary prevention in ESUS is thus relevant to large numbers of stroke patients.

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Figure legend: Frequency of embolic strokes of undetermined source (ESUS) as a proportion of all ischemic strokes. An unknown number of those with incomplete diagnostic testing were likely to be ESUS.

Table 1. Diagnostic criteria for embolic stroke of undetermined source (ESUS)*

1. Stroke visualized by CT or MRI that is not lacunar†
2. Absence of extracranial or intracranial atherosclerosis causing $\geq 50\%$ luminal stenosis or occlusion of arteries supplying the area of ischemia#
3. No major-risk cardioembolic source of embolism^ by history, ECG, echocardiography and ≥ 24 hours of cardiac rhythm monitoring
4. No other specific cause of ischemic stroke identified (e.g, arteritis, dissection, migraine/vasospasm, drug abuse)

CT = computed tomography; MRI = magnetic resonance imaging; ECG = electrocardiogram.

* Cryptogenic Stroke / ESUS International Working Group definition.(1)

†Lacunar defined as a subcortical infarct ≤ 1.5 cm (≤ 2.0 cm on MRI diffusion images) in largest dimension.

Requires extracranial and intracranial arterial imaging using sonography, CT angiography or MR angiography of the relevant arteries.

^Permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, mechanical prosthetic cardiac valve, atrial myxoma or other cardiac tumors, moderate/severe mitral stenosis, recent (<4 weeks) myocardial infarction, valvular vegetations, or infective endocarditis.

Table 2: Frequency of ESUS patients by country

City, Country	Ischemic strokes		ESUS* n (%)
	N	Mean age (years)	
Buenos Aires, Argentina	73	68	24 (33%)
Perth, Australia	114	67	24 (21%)
Brussels, Belgium	119	74	17 (14%)
Sao Paulo, Brazil	86	60	15 (27%)
Hamilton, Canada	172	73	29 (17%)
Beijing, China	69	59	11 (16%)
Paris, France	69	69	25 (36%)
Heidelberg, Germany	91	73	18 (20%)
Galway, Ireland	140	71	10 (7%)
Rome, Italy	91	67	19 (21%)
Tokyo, Japan	75	68	18 (24%)
Mexico City, Mexico	225	56	21 (9%)
Amsterdam, Netherlands	99	68	1 (1%)
Manila, Philippines	175	62	23 (13%)
Coimbra, Portugal	123	74	23 (19%)
Moscow, Russia	106	66	24 (23%)
Seoul, Korea	124	69	26 (21%)
Glasgow, United Kingdom	73	67	5 (7%)
Philadelphia, United States	120	67	18 (15%)
Total	2144	67	351 (16%)

*ESUS = embolic stroke of undetermined source. See Table 1 for criteria.

Table 3. Frequency of ESUS patients by global region

Region	Ischemic strokes N	ESUS patients* N (%)
Europe (9 sites)	911	142 (16%)
North America (2 sites)	292	47 (16%)
Latin America (3 sites)	384	60 (16%)
East Asia (3 sites)	268	55 (21%)
Pacific^ (2 sites)	289	47 (16%)
All regions	2144	351 (16%)

*ESUS = embolic stroke of undetermined source. See Table 1 for criteria.

^Australia and Philippines.

Table 4. Clinical features of ESUS patients overall and by global region*

	All ESUS patients (n=351)	ESUS patients by Global Region				
		Europe (n=142)	North America (n=47)	Latin America (n=60)	East Asia (n=55)	Pacific (n=47)
Mean age, yrs (SD)	62 (15)	65 (15)	63 (13)	59 (17)	56 (15)	61 (14)
Men, %	57	60	51	42	78	51
Diabetes mellitus, %	25	23	34	17	29	26
Hypertension, %	64	63	89	56	56	63
Coronary artery disease, %	10	11	15	5	0	28
Current tobacco smoking, %	26	18	31	13	53	28
Heart failure, %	2	4	0	0	0	0
Peripheral vascular disease, %	3	4	34	5	0	0
Antiplatelet therapy at index stroke, %	31	26	32	28	15	66
Anticoagulant therapy at index stroke, %	1	2	0	2	0	2
Estimated GFR <30 mL/min, %	1	0	0	0	5	0
Clinical stroke or TIA prior to index stroke, %	17	15	17	20	15	22
Old ischemic stroke on CT, %	32	31	44	35	29	17
Old ischemic stroke on MRI, %	40	33	51	39	31	56
Patent foramen ovale (precordial echo), %	6	6	0	15	4	9
Transesophageal echocardiography (TEE)						
Patent foramen ovale by TEE, %	25	27	25	42	17	25
Aortic arch plaque by TEE, %	29	37	50	15	11	25
Complex/ulcerated aortic plaque by TEE, %	6	9	13	0	0	0
i.v. tPA for index stroke, %	16	24	19	10	7	11
Median NIH Stroke Scale score \leq 48 hours of stroke onset (IQR)	4 (2,8)	5 (3,10)	6 (3,9)	4 (1,6)	2 (1,5)	4 (3,6)
Modified Rankin Scale near discharge (SD)	2 (1)	2 (1)	2 (3)	2 (1)	1 (1)	-
Death within 30 days, %	2	3	4	0	0	4
Any contraindication to anticoagulation, %	9	8	15	8	9	9
Antiplatelet therapy at hospital discharge, %	90	92	87	90	93	85
Anticoagulation at hospital discharge, %	6	4	13	8	7	4

ESUS = embolic stroke of undetermined source; GRF = glomerular filtration rate; NIH = National Institutes of Health; tPA = tissue plasminogen activator, IQR = interquartile range.

*Due to missing values, completeness of data ranges from 76% to 99% for the second column.

Table 5. Frequency of minor-risk embolic sources among ESUS patients

Minor-risk potential embolic sources*	N (%)
Cervical carotid artery non-stenotic plaques**	208 (79%)
Mitral valve disease: annular calcification and/or thickening with myxomatous changes [#]	17 (5%)
Aortic valve disease: stenosis and/or calcification [#]	24 (7%)
Hypokinetic/ akinetic left ventricle [#]	13 (4%)
Moderate-to-severely dilated left atrium [#]	19 (6%)
Aortic arch atherosclerotic plaques [^]	35 (28%)
Patent foramen ovale [#]	19 (6%)
Patent foramen ovale [^]	31 (25%)
Any minor-risk embolic source ^{^^}	258 (74%)
≥2 minor-risk embolic sources	83 (24%)

* Minor-risk embolic sources are those associated with a relatively low absolute rate of stroke such that they are often incidentally present when identified in a stroke patient rather than the stroke cause, and consequently have unclear management implications.(1)

** Excluding those with posterior circulation ischemia.

Those who underwent transthoracic echocardiography

[^] Those who underwent transeophageal echocardiography.

^{^^} Excluding carotid artery plaques as a minor-risk source, the 35% (n=122) had one or more minor-risk sources..

